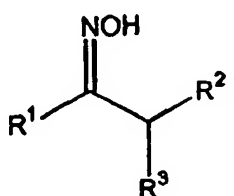




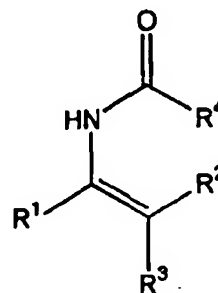
## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup>:</b>  <b>C07C 231/18</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 99/18065</b>  <b>(43) International Publication Date:</b> 15 April 1999 (15.04.99)
<b>(21) International Application Number:</b> PCT/GB98/02966 <b>(22) International Filing Date:</b> 2 October 1998 (02.10.98)  <b>(30) Priority Data:</b> 9721087.6                      3 October 1997 (03.10.97)                      GB 9722583.3                      24 October 1997 (24.10.97)                      GB 9806916.4                      31 March 1998 (31.03.98)                      GB  <b>(71) Applicant:</b> CHIROTECH TECHNOLOGY LIMITED [GB/GB]; Cambridge Science Park, Milton Road, Cambridge CB4 4WE (GB).  <b>(72) Inventors:</b> JOHNSON, Nicholas, Bernard; Chirotech Technology Limited, Cambridge Science Park, Milton Road, Cambridge CB4 4WE (GB). BURK, Mark, Joseph; Chirotech Technology Limited, Cambridge Science Park, Milton Road, Cambridge CB4 4WE (GB). CASY, Guy; Chirotech Technology Limited, Cambridge Science Park, Milton Road, Cambridge CB4 4WE (GB).  <b>(74) Agent:</b> GILL JENNINGS & EVERY; Broadgate House, 7 Eldon Street, London EC2M 7LH (GB).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>

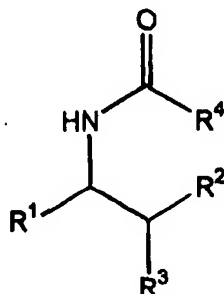
(54) Title: CHIRAL AMINES



(2)



(4)



(5)

## (57) Abstract

An efficient synthesis of chiral amines (5) comprises preparing an enamide (4) from the oxime (2), and subjecting the enamide to catalytic asymmetric hydrogenation.

*FOR THE PURPOSES OF INFORMATION ONLY*

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

## CHIRAL AMINES

### Field of the Invention

This invention relates to processes suitable for the large-scale preparation of enantiomerically-enriched chiral amines.

### 5 Background to the Invention

Enantiomerically-enriched chiral primary amines are of great interest for a variety of reasons. Readily available chiral amines such as  $\alpha$ -methylbenzylamine are used commonly as resolving agents for racemic acids [Paul Newman, "Optical Resolution Procedures for Chemical Compounds", Volume 2, Acids, Part 1 and 2, Optical Resolution  
10 Information Center, New York, 1981].

In addition to widespread application in optical resolutions, chiral amines are used extensively as chiral auxiliaries for asymmetric synthesis [J. Seyden-Penne, "Chiral Auxiliaries and Ligands in Asymmetric Synthesis," John Wiley & Sons, 1995]. Moreover, the utility of chiral amines as ligands for transition metals in asymmetric catalysis has been  
15 amply demonstrated [T. Ohkuma *et al*, *J. Am. Chem. Soc.* (1995), 117:, 2675]. Finally, many current and emerging pharmaceuticals contain chiral amines as constituent parts and hence their preparation is of great interest to the pharmaceutical industry.

A problem exists in that there is not a great diversity of chiral amines available on a commercial basis. A process which allows ready access to a wide range of such amines  
20 could satisfy the manifold applications for chiral amines, e.g. to allow preparation of resolving agents which could be tailored to specific resolutions. Particularly valuable would be a process that allowed the preparation of either amine enantiomer with equal facility from prochiral starting materials.

There are various methods available for the preparation of enantiomerically-  
25 enriched amines, few of which are amenable to large-scale preparation. Many examples involving asymmetric synthesis have been reported. For example, the addition of organometallic reagents to imines or their derivatives is reported by Itsuno *et al*, *Tetrahedron Asymm.* (1995) 6:1507; Watanabe *et al*, *Tetrahedron Asymm.* (1995) 6:1531; Denmark *et al*, *J. Am. Chem. Soc.* (1987) 109:2224; Takahashi *et al*, *Chem. Pharm. Bull.* (1982) 30:3160; and the addition of organometallic reagents to chiral oxazolidines is  
30 disclosed by Mokhallalati *et al*, *Tetrahedron Lett.* (1994) 35:4267. These procedures have

been widely employed, but are not readily applicable to large-scale production due to costly reagents and extreme reaction conditions (e.g. reactions at -78°C).

Other approaches include optical resolution which may be conducted through biotransformations or by the formation of diastereomeric salts that are separated by crystallisation methods. These methods are deficient for a number of reasons. Often they are appropriate for the preparation of only one of the two possible stereoisomers, due to the ready availability of only one enantiomer of chiral acid or appropriate enzyme. Also, resolution processes, by definition, afford a maximum of 50% yield of the desired stereoisomer; the opposite stereoisomer must be discarded or recycled [Paul Newman, "Optical Resolution Procedures for Chemical Compounds," Volume 1, Amines and Related Compounds, Optical Resolution Information Center, New York, 1981]. Hence, resolution processes are notoriously inefficient and generate substantial waste.

The preparation of enantiomerically-enriched amines recently has been described by Burk *et al*, *J. Am. Chem. Soc.* (1996) 118:5142. This process comprises the asymmetric hydrogenation of certain prochiral *N*-acetyl or aryl enamides to give *N*-acetyl or arylalkylamines, with high enantioselectivities. Simple hydrolytic deprotection then affords chiral amines. Although this potentially is an excellent and unique method for the production of chiral amines from prochiral *N*-acetyl enamides, the process was severely limited by the method employed to prepare the enamide precursors. These were accessed by addition of alkyl Grignard reagents to aryl nitriles, followed by the addition of acetic anhydride. The enamide products were obtained in low yield (20-40 %) after a tedious purification procedure involving column chromatography and crystallisation. This process clearly was unsuitable for large-scale production of *N*-acetyl enamides, and hence not applicable to the commercial preparation of chiral amines *via* asymmetric hydrogenation.

Other methods for the preparation of enamides have been described. The Beckmann rearrangement has been used to prepare enamides from unsaturated oximes or their derivatives, but these processes are not very general, nor are they suitable for large scale preparations. See Mukaiyama and Harada, *Chem. Lett.* (1991) 1653; Harada *et al*, *Synthesis* (1991) 1216; and Redeker *et al*, *Tetrahedron Lett.* (1981) 22:4263.

A singular example entailing reduction of a steroidal oxime to the corresponding acetyl enamide by heating with Fe and acetic anhydride at 100°C is described by Barton and Zard, *J. Chem. Soc. Perkin Trans. 1* (1985) 2191. However, our attempts to repeat

this procedure gave only moderate yields of impure enamides which required arduous purification. The process was not suitable for the preparation of *N*-acetyl enamides for homogeneous asymmetric hydrogenation, as impurity levels remained too high and inhibited catalysis from proceeding. Moreover, the process as described is not general,  
5 since the steroidal oxime was not prepared from a ketone.

US-A-4194050 describes the reduction of oximes to *N*-acetyl enamides using Ru-on-carbon and hydrogen in acetic anhydride. Attempts to reproduce this oxime reduction procedure have resulted in the formation of fully reduced mono- and di-acetyl amines.

The preparation of *N*-acetyl enamides using the Fe and acetic anhydride reduction  
10 of nitro olefins is reported by Laso *et al*, *Tetrahedron Lett.* (1996) 37:1605. Again, the procedure is not applicable to large-scale production of assorted *N*-acetyl enamides due to the limited availability of the precursor nitro olefins.

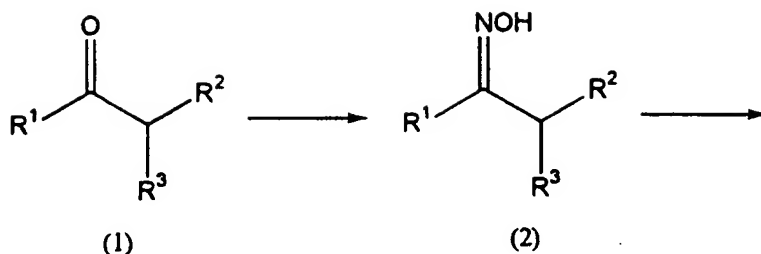
More esoteric approaches have included the copper iodide-promoted vinylic substitution of vinyl bromides with primary amides [Ogawa *et al*, *Chem Lett.*, 1991, 1433]  
15 and the copper-catalysed decarboxylation of dehydroamino acid derivatives [Schmidt and Lieberknecht, *Angew. Chem. Int. Ed. Engl.* (1983) 22:550].

#### Summary of the Invention

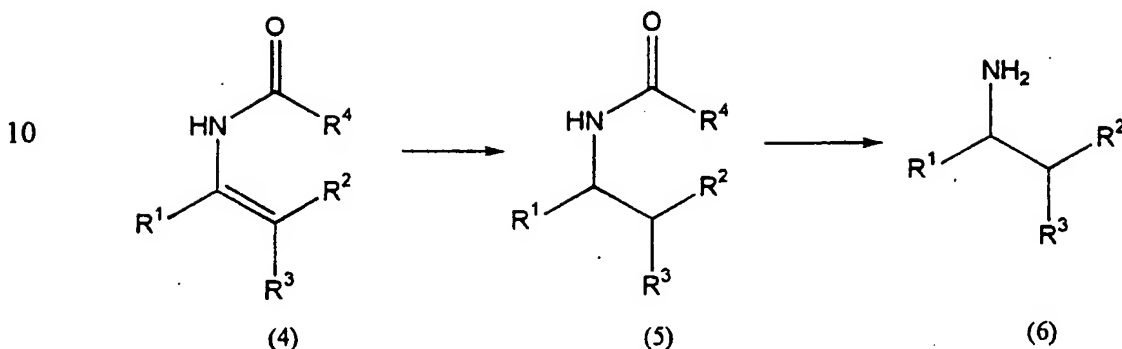
This invention is based on the discovery that ketones and aldehydes can be readily transformed into enantiomerically-enriched chiral amines. This process is amenable to  
20 large-scale production, and involves the metal-mediated reduction of oxime intermediates to form enamides. These enamides are formed in high yields and in a high initial state of purity. The enamides thus produced are suitable substrates for homogeneous asymmetric hydrogenation using transition metal catalyst systems. The next step of the process, asymmetric hydrogenation of enamides, results in the formation of highly  
25 enantiomerically-enriched amides, which may be deprotected readily to furnish valuable enantiomerically-enriched amines. Either enantiomer of the amine may be obtained by this method.

The steps of the reaction are shown below. This invention relates to a combination of the enamide formation and asymmetric hydrogenation steps at least.

4



5



10

15 An additional aspect of this invention lies in the discovery that, perhaps most evidently for compounds including a ring structure formed by  $\text{R}^1$  and  $\text{R}^3$ , reduced temperature in the asymmetric hydrogenation step may provide enhanced enantiomeric excess (ee). Another aspect lies in certain novel enamides, of the type wherein  $\text{R}^1$  is non-enolisable.

## 20 Description of the Invention

Ketones and aldehydes which can be used as readily available starting materials for the novel process are of formula (1).  $\text{R}^1$ ,  $\text{R}^2$  and  $\text{R}^3$  are each together or independently H (hydrogen) or any organic group of up to 30 carbon atoms, with the proviso that when  $\text{R}^1=\text{H}$ ,  $\text{R}^2$  and  $\text{R}^3$  are different groups and neither is H. Further,  $\text{R}^1$  and  $\text{R}^3$  together, and/or
   
 25  $\text{R}^2$  and  $\text{R}^3$  together, may form a ring or rings (which term includes mono-, di- and higher polycyclic ring systems). Examples of ketones (1) in which  $\text{R}^1$  and  $\text{R}^3$  form a ring are indanones and tetralones, e.g.  $\alpha$ -tetralone and  $\beta$ -tetralone; for the tetralones, it is preferred that the asymmetric hydrogenation is conducted at below  $20^\circ\text{C}$ , more preferably at or below  $10^\circ\text{C}$ .

30 It may be preferred that  $\text{R}^1$  and  $\text{R}^3$  are independent, such that the carbonyl C atom is not in a ring. Another preference is that  $\text{R}^2$  and/or  $\text{R}^3$  is H. If the enamide (4) is trisubstituted, it may be used as a mixture of geometric isomers.  $\text{R}^1$  is preferably an aryl,

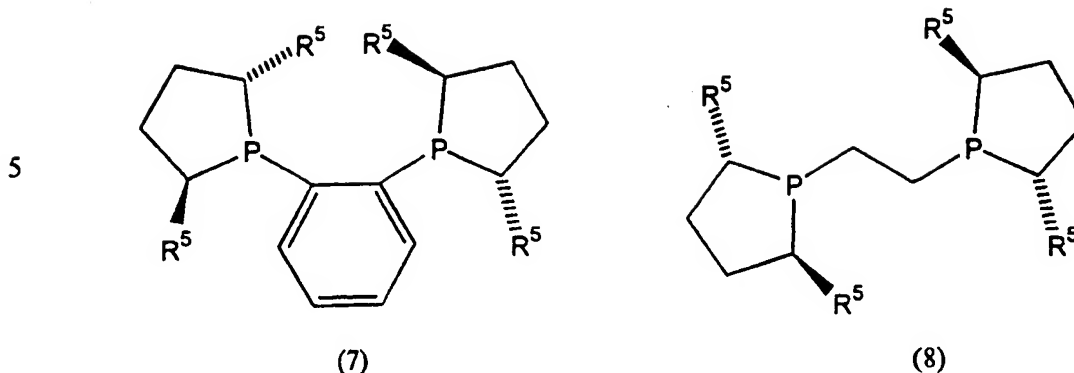
heteroaryl or unsaturated aliphatic group, including *tert*-alkyl, e.g. *tert*-butyl, and adamantyl;  $R^1$  may also be trihalomethyl, e.g.  $CF_3$ .

The corresponding oximes (2) of these carbonyl compounds (1) are readily prepared by reaction with hydroxylamine under a variety of conditions, and this transformation is well known [Sandler and Karo, "Organic Functional Group Preparations," vol 3, pp 372-381, Academic Press, New York, 1972]. Thus, treating carbonyl compounds (1) with hydroxylamine hydrochloride and solvent, e.g. with sodium acetate in ethanol, followed by partitioning between TBME and water, affords oximes of the type (2) in high yield. These oximes (2) then are transformed by heating with a reducing metal  $M^1$ , in the presence of an acylating agent of the formula  $(R^4CO)_2O$  or  $R^4COX$  (3), wherein  $R^4$  is independently H or any organic group of up to 30 carbon atoms, and X is a leaving group. This gives after a basic aqueous work-up, enamides of the formula (4). For example, a suitable combination of reducing metal  $M^1$ , acylating agent, acid and solvent is: Fe, acetic anhydride, acetic acid and toluene.

Various reaction parameters are preferred in the oxime reduction step. For instance, performing the reaction at moderate temperatures ( $\leq 75^\circ C$ ) attenuates otherwise problematic product decomposition. Also, the introduction of an acid, e.g. acetic acid (3 equiv/mol of oxime), leads to enhancement of the oxime reduction rates. Finally, the use of a cosolvent (e.g., toluene), under these conditions, greatly facilitates product isolation. The initial reduction mixture generally consists of both monoacetyl and diacetyl (assuming acetic acid is used) products that, through a simple 2 M NaOH wash, are converged into the desired monoacetyl enamides (4) in moderate to good yields (40-85%, unoptimized) and importantly in a high state of purity.

The enamides (4) are then subjected to homogeneous asymmetric hydrogenation, e.g. with a chiral catalyst,  $H_2$  and solvent, preferably using catalyst systems derived from the complex of a transition metal  $M^2$  with a chiral phosphine ligand. This results in the formation of enantiomerically enriched *N*-acyl amines (5). Typically, the enamide (4) is subjected to reduction in a solvent, preferably in the presence of an acid, with an asymmetric catalyst and hydrogen, to afford directly after evaporation the acyl amine (5).

By way of example, the catalyst is a complex of a transition metal and a chiral bis-phosphine of formula (7) or (8)



10

(or the opposite enantiomer thereof), wherein  $R^5$  is any non-hydrogen organic group, e.g. of up to 20 or 30 C atoms, preferably  $C_{1-4}$  linear or branched alkyl.  $M^2$  is preferably Rh, Ru or Ir.

When using rhodium catalyst systems such as those described in US-A-5171892 and US-A-5532395, e.g. those derived from 1,2-bis(phospholano)benzene (DuPHOS) or 1,2-bis(phospholano)ethane (BPE) ligands, the enantiomeric purity of the amines is uniquely high and generally exceeds 90% ee. For example, the enamide (4), where  $R^1$  is 2-naphthyl,  $R^2$  and  $R^3$  are H and  $R^4$  is Me, is hydrogenated at about 415 kPa (60 psi) hydrogen pressure using 0.2 mol% of a Rh-Me-DuPHOS catalyst in methanol, to give the *N*-acetyl amine (5) where  $R^1$  is 2-naphthyl,  $R^2$  and  $R^3$  are H and  $R^4$  is Me in 92% ee. In a second example, the enamide (4), where  $R^1$  is *tert*-butyl,  $R^2$  and  $R^3$  are H and  $R^4$  is Me, was hydrogenated at 1380 kPa (200 psi) hydrogen pressure using 0.1 mol% of a Rh-Me-DuPHOS catalyst in methanol, to give the *N*-acetyl amine (5) where  $R^1$  is *tert*-butyl,  $R^2$  and  $R^3$  are H and  $R^4$  is Me in >98% ee.

25 These *N*-acyl amines (5) can then be deprotected using suitable conditions depending upon the nature of  $R^4$  to give enantiomerically-enriched amines (6) where  $R^1$ ,  $R^2$  and  $R^3$  are as defined previously. Moreover, for enamides (4) which are generated as a mixture of geometric isomers, asymmetric hydrogenation using catalysts based on the DuPHOS and BPE ligand series results in enantioconvergent conversion of *E*- and *Z*- isomers.

30



The following Examples illustrate the invention. In each case, parts A, B and C respectively illustrate the first 3 steps shown above, i.e. formation of the oxime, formation of the enamide, and asymmetric hydrogenation. TBME is *tert*-butyl methyl ether.

**Example 1**  $R^1 = 2\text{-naphthyl}$ ,  $R^2=R^3=H$ ,  $R^4=CH_3$

5 A. Sodium acetate (307 g, 3.7 mol) was added to a solution of 2'-acetonaphthone (525 g, 3.08 mol) in ethanol (2.0 L) followed by hydroxylamine hydrochloride (236 g, 3.4 mol). After stirring for 4 days, the reaction was diluted with TBME (1.0 L) and washed with water (2 x 1 L). The organic phase was then partially evaporated and the resultant suspension was then allowed to stand for 18 h, and filtered to give 2'-acetonaphthone  
10 oxime (530 g, 93%).

B. Acetic anhydride (320 ml) and acetic acid (130 ml) were added to a suspension of 2'-acetonaphthone oxime (123 g, 0.66 mol) in toluene (450 ml) and allowed to stir under nitrogen. Fe powder (74.3 g, 1.33 mol) was then added and the mixture heated at 70-75°C for 3 h. The reaction was then cooled to room temperature and filtered through  
15 Celite to remove solid residues. These residues were washed with toluene (4 x 100 ml). The combined organic extracts were then cooled in an ice-bath and washed with 2 M NaOH (1 L batches) until the aqueous phase remained at pH 14. This final biphasic mixture was then allowed to stir for 0.5 h, during which time a precipitate formed. Water (0.5 L) then was added and the solid was filtered to give *N*-acetyl-1-(2-naphthyl)-1-ethenamine (97 g, 70%).  
20

C. Degassed methanol (300 ml) was added to *N*-acetyl-1-(2-naphthyl)-1-ethenamine (30.0 g, 142 mmol) and [(COD)Rh(*R,R*)-Me-DuPHOS]BF<sub>4</sub> (0.086 g, 0.14 mmol) in a 600 ml Parr pressure vessel, purged with hydrogen. The reactor then was purged further with hydrogen (three times), charged to 1380 kPa (200 psi) hydrogen and allowed to stir for  
25 24 h. Subsequent evaporation of the solvent yielded (*R*)-*N*-acetyl-1-(2-naphthyl)ethanamine (29.46 g, 97%) with 92.2% enantiomeric excess.

**Example 2**  $R^1 = \textit{tert}\text{-butyl}$ ,  $R^2=R^3=H$ ,  $R^4=CH_3$

A. Sodium acetate (49.8 g, 600 mmol) was added to a solution of pinacolone (50.0 g, 500 mmol) in ethanol (200 ml) followed by hydroxylamine hydrochloride (38.2 g, 550  
30 mmol). After stirring for 2.5 h the reaction was diluted with TBME (200 ml) and washed with water (2 x 200 ml) and brine (200 ml). The organic phase was then dried (MgSO<sub>4</sub>) and partially evaporated to ~100 ml volume and the resultant suspension was then allowed

to stand for 18 h. The crystalline solid was then filtered to give pinacolone oxime (33.0 g, 50%).

B. Acetic anhydride (80 ml) and acetic acid (50 ml) were added to a solution of pinacolone oxime (33.0 g, 286.5 mmol) in toluene (300 ml) and the mixture allowed to stir  
5 under nitrogen. Fe powder (32.0 g, 573 mmol) was then added and the mixture heated at 70 °C for 4.5 h. The reaction was then cooled to 50 °C and filtered through Celite to remove solid residues. These residues were washed with toluene (100 ml). The combined organic extracts were then cooled in an ice-bath and washed with 2 M NaOH (500 ml) and then with further 2M NaOH (200 ml) such that the aqueous phase remained at pH 14.  
10 This final biphasic mixture was then allowed to stir for 0.25 h. The organic phase was then separated, dried (MgSO<sub>4</sub>) and evaporated to give *N*-acetyl-1-(*tert*-butyl)-1-ethenamine (20.3 g, 50%).

C. Degassed methanol (10 ml) was added to *N*-acetyl-1-(*tert*-butyl)-1-ethenamine (0.5 g, 3.5 mmol) and [(COD)Rh(*R,R*)-Me-DuPHOS]BF<sub>4</sub> (0.0021 g, 0.0035 mmol) in a 50 ml  
15 Parr pressure vessel, purged with hydrogen. The reactor then was purged further with hydrogen (three times), charged to 1380 kPa (200 psi) hydrogen and allowed to stir for 2.5 h. Subsequent evaporation of the solvent yielded *N*-acetyl-1-(*tert*-butyl)ethanamine (0.48 g, 96%) with >98% enantiomeric excess.

**Example 3** R<sup>1</sup> = phenyl, R<sup>2</sup> = R<sup>3</sup> = R<sup>4</sup> = CH<sub>3</sub>

A. Sodium acetate (67.2 g, 675 mmol) was added to a solution of isobutyrophenone  
20 (100.0 g, 675 mmol) in ethanol (200 ml) followed by hydroxylamine hydrochloride (51.6 g, 742 mmol). After stirring for 5 h the reaction was partitioned between TBME (300 ml) and water (300 ml). The organic phase was separated and washed with sat. NaHCO<sub>3</sub> (3 x 200 ml) and brine (200 ml), dried (MgSO<sub>4</sub>) and evaporated to give isobutyrophenone  
25 oxime (98.8 g, 90%). <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 7.25-7.5 (m, 5H), 3.6 (m, 0.6H), 2.85 (m, 0.4H), 1.1-1.2 (m, 6H).

B. Acetic anhydride (8.7 ml) and acetic acid (5.2 ml) were added to a solution of isobutyrophenone oxime (5.0 g, 30.6 mmol) in toluene (60 ml) and the mixture allowed to stir under nitrogen. Fe powder (3.4 g, 61.2 mmol) was then added and the mixture  
30 heated at 70°C for 4 h. The reaction was then cooled and filtered through Celite to remove solid residues. These residues were washed with toluene (10 ml). The combined organic filtrates were then cooled in an ice-bath and washed with 2 M NaOH (2 x 50 ml).

The organic phase was then dried ( $\text{MgSO}_4$ ) and evaporated to ~15 ml volume, heptane (15 ml) was then added causing crystallisation. The solid was then filtered to give the enamide (3.43 g, 60%).  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ) (2:1 mixture of rotamers)  $\delta$  7.25-7.5 (m, 5H), 6.6-6.85 (br m, 1H), 2.11 (s, 2H), 1.75-2.0 (m, 7H).

- 5 C. Unsurprisingly, hydrogenation of this tetra-substituted double bond has proved to be more difficult than for other examples of the invention. Without optimisation, 20% ee has been achieved using the same catalyst as in Example 2(C).

**Example 4**  $\text{R}^1 = 1\text{-adamantyl}$ ,  $\text{R}^2=\text{R}^3=\text{H}$ ,  $\text{R}^4 = \text{CH}_3$

- A. Sodium acetate (14.0 g, 168 mmol) was added to a solution of 1-adamantyl methyl ketone (25.0 g, 140 mmol) in ethanol (150 ml) followed by hydroxylamine hydrochloride (10.7 g, 154 mmol). After stirring for 18 h the reaction was partitioned between TBME (250 ml) and water (200 ml). A solid formed which was filtered off. The organic phase was separated and washed with water (2 x 200 ml) and brine (200 ml), dried ( $\text{MgSO}_4$ ) and partially evaporated to ~100 ml volume and the resultant suspension was then allowed to stand for 18 h. The crystalline solid was then filtered and combined with the previous solid to give 1-adamantyl methyl ketone oxime (12.55 g, 77%).  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  9.55 (br s, 1H), 1.5-2.1 (m, 18H).

- B. Acetic anhydride (7.5 ml) and acetic acid (4.3 ml) were added to a solution of 1-adamantyl methyl ketone oxime (5.0 g, 25.9 mmol) in toluene (50 ml) and the mixture allowed to stir under nitrogen. Fe powder (2.88 g, 51.5 mmol) was then added and the mixture heated at 70°C for 8 h. The reaction was then cooled and filtered through Celite to remove solid residues. These residues were washed with toluene (10 ml). The combined organic extracts were then cooled in an ice-bath and washed with 2 M NaOH (2 x 50 ml). The organic phase was then dried ( $\text{MgSO}_4$ ) and evaporated. The resultant product was then subjected to chromatographic purification (silica - 60 mesh) using 25% EtOAc in pentane as eluent, to give *N*-(1-Adamantan-1-yl-ethyl)acetamide (2.4 g, 43%).  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  6.49 (br s, 1H), 5.62 (br s, 1H), 4.75 (br s, 1H), 1.6-2.2 (br m, 18H).

- C. *N*-(1-Adamantan-1-ylvinyl)acetamide (0.5 g, 2.28 mmol) and  $[(R,R)\text{-Me-DuPHOS}]\text{-Rh}(\text{COD})\text{BF}_4$  (2.8 mg, 0.2 mol%) are placed in a glass-lined 50 ml pressure vessel, which was then purged with hydrogen [1380 kPa (200 psi) x 3]. Degassed methanol (10 ml; sparged with nitrogen for 2 h) was then added and the vessel further

purged with hydrogen [1380 kPa (200 psi) x 2] and charged to 1380 kPa (200 psi) hydrogen. After stirring for 20 h, the reaction mixture was evaporated to afford a residue. This residue was dissolved in EtOAc (5 ml) and the solution filtered through a short silica plug to remove catalyst residues. The solvent was then evaporated to afford (*S*)-*N*-(1-  
5 adamantan-1-ylethyl)acetamide (0.49 g, 97% yield) as a white solid.

Enantiomeric excess: >99% by chiral HPLC

<sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ. 5.42 (d, <sup>3</sup>J = 10 Hz, 1H), 3.7 (dt, <sup>33</sup>J = 10 / 7 Hz, 1H), 2.15 - 1.40 (m, 18H), 1.02 (d, <sup>3</sup>J = 7 Hz, 3H).

<sup>13</sup>C-NMR (CDCl<sub>3</sub>): δ 169.45 (CO), 52.98 (HCN), 38.36 (CH<sub>2</sub>), 37.05 (CH<sub>2</sub>), 35.69 (C),  
10 28.44 (CH), 23.65 (CH<sub>3</sub>CO), 14.57 (CH<sub>3</sub>CH).

**Example 5**  $R^1 + R^3 = \alpha$ -tetralone,  $R^2 = H$ ,  $R^4 = CH_3$

A. Sodium acetate (68.1 g, 821 mmol) was added to a solution of  $\alpha$ -tetralone (100.0 g, 684 mmol) in ethanol (200 ml) followed by hydroxylamine hydrochloride (52.3 g, 752 mmol). After stirring for 5.5 h, the reaction was partitioned between TBME (250 ml) and  
15 water (200 ml). The organic phase was separated and washed with water (2 x 200 ml) and brine (200 ml), dried (MgSO<sub>4</sub>) and partially evaporated to ~250 ml volume and the resultant suspension was then allowed to stand for 18 h. The crystalline solid was then filtered to give  $\alpha$ -tetralone oxime (89.37 g, 81%). <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 9.05 (br s, 1H), 7.85-7.95 (m, 1H), 7.1-7.4 (m, 3H), 2.7-3.0 (m, 4H), 1.8-2.0 (m, 2H).

20 B. Acetic anhydride (80 ml) and acetic acid (48 ml) were added to a solution of  $\alpha$ -tetralone oxime (45.0 g, 279 mmol) in toluene (400 ml) and the mixture allowed to stir under nitrogen. Fe powder (31.2 g, 558 mmol) was then added and the mixture heated at 70°C for 4 h. The reaction was then cooled to 50°C and filtered through Celite to remove solid residues. These residues were washed with toluene (2 x 100 ml). The  
25 combined organic extracts were then cooled in an ice-bath and washed with 2 M NaOH (2 x 300 ml). The organic phase was then dried (MgSO<sub>4</sub>) and the product allowed to crystallise. This was filtered to give *N*-(3,4-dihydronaphthalen-1-yl)-acetamide (28.0 g, 54%). <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) (3:1 mixture of rotamers) δ 7.05-7.3 (m, 4H), 6.7-7.05 (br m, 1H), 6.42 (t, 0.75H), 5.95 (br t, 0.25H), 2.65-2.95 (m, 2H), 2.25-2.5 (m, 2H), 2.15  
30 (s, 2.25H), 1.95 (s, 0.75H).

C. *N*-(3,4-Dihydronaphthalen-1-yl)acetamide (0.5 g, 2.67 mmol) was placed in a glass lined 50 ml pressure vessel, which was then purged with hydrogen [1380 kPa (200 psi) x

3]. Degassed methanol (10 ml) was then added and the vessel further purged with hydrogen [1380 kPa (200 psi) x 2] and charged to 1380 kPa (200 psi) hydrogen and then cooled such that the internal temperature was 0 °C. The vessel was then vented and [((*S,S*)-Me-BPE)-Rh-(COD)]OTf (3.2 mg, 0.2 mol%) in degassed methanol (0.5 ml) added, the vessel was then repressurised to 1380 kPa (200 psi). After stirring for 20 h, the reaction mixture was evaporated to afford a residue. This residue was dissolved in EtOAc (5 ml) and the solution filtered through a short silica plug to remove catalyst residues. The solvent was then evaporated to afford (*S*)-*N*-(1,2,3,4-tetrahydronaphthalen-1-yl)acetamide (0.49 g, 99%) as a tan solid.

10 Enantiomeric excess: 92% by chiral GC

<sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.04 - 7.30 (m, 4H), 5.87 (brd, 1H), 5.10 - 5.20 (m, 1H), 2.68 - 2.86 (m, 2H), 1.90 - 2.08 (m, 2H), 2.00 (s, 3H), 1.72 - 1.88 (m, 2H).

<sup>13</sup>C-NMR (CDCl<sub>3</sub>): δ 169.27 (CO), 137.57 (C-bridge head), 136.65 (C-bridge head), 129.15 (Ar), 128.73 (Ar), 127.26 (Ar), 126.21 (Ar), 47.42 (HCN), 30.07 (CH<sub>2</sub>), 29.20 (CH<sub>2</sub>), 23.50 (CH<sub>3</sub>), 19.88 (CH<sub>2</sub>).

For the purpose of comparison, similar experiments were performed using internal temperatures of 10°C, 20°C and 50°C. Products obtained from these experiments had enantiomeric excesses of 90%, 69% and 54% respectively.

**Example 6**  $R^1 + R^3 = 3H\text{-inden-1-yl}$ ,  $R^2 = H$ ,  $R^4 = CH_3$

20 B. Acetic anhydride (10.4 g, 102 mmol), followed by acetic acid (6.1 g, 102 mmol), was added to a solution of 1-indanone oxime (5.0 g, 34 mmol) in toluene (50 ml), under a nitrogen atmosphere. Fe powder (Aldrich; 325 mesh) (3.8 g, 68 mmol) was then added and the mixture heated to 70 °C for 0.25 h. The reaction was then cooled to room temperature and filtered through Celite to remove solid residues which subsequently were washed with toluene (2 x 10 ml). The combined filtrates were cooled in an ice-bath and washed with 2M NaOH (2 x 50 ml). The organic phase was then separated, dried (MgSO<sub>4</sub>) and evaporated to afford a residue. This was purified by column chromatography (SiO<sub>2</sub> 60-mesh, 100g) (40% EtOAc in pentane as eluent) to afford *N*-(3H-inden-1-yl)acetamide as a tan solid (1.80 g, 30% yield).

30 <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.40 - 7.56 (m, 2H), 7.16 - 7.34 (m, 3H), 6.88 (brt, 1H), 3.44 (m, 2H), 2.25 (s, 3H).

$^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ ): 168.60 (CO), 142.84 (CN), 139.64 (C-bridge head), 135.32 (C-bridge head), 125.99 (CH), 125.44 (CH), 124.31 (CH), 115.99 (CH), 115.73 (CH), 36.57 ( $\text{CH}_2$ ), 24.22 ( $\text{CH}_3$ ).

- C. *N*-(3*H*-Inden-1-yl)acetamide (0.5 g, 2.84 mmol) and [(*S,S*)-Me-BPE)-Rh-(COD)]OTf (3.5 mg, 0.2 mol%) are placed in a glass-lined 50 ml pressure vessel, which was then purged with hydrogen [1380 kPa (200 psi) x 3]. Degassed methanol (10 ml; sparged with nitrogen for 2 h) was then added and the vessel further purged with hydrogen 1380 kPa (200 psi) x 2] and charged to 1380 kPa (200 psi) hydrogen. After stirring for 20 h, the reaction mixture was evaporated to afford a residue. This residue was dissolved in EtOAc (5 ml) and the solution filtered through a short silica plug to remove catalyst residues. The solvent was then evaporated to afford (*S*)-*N*-indan-1-ylacetamide (0.49 g, 99% yield) as a tan solid. Absolute stereochemical assignment was achieved by comparison of the sign of optical rotation and chiral gc elution order with a standard sample prepared by acetylation of authentic (*S*)-1-aminoindane (commercially available; Lancaster Chemicals) using  $\text{Ac}_2\text{O}$ /pyridine.
- $[\alpha]_D^{20} = -122.4$  (c 1.0, MeOH).

Enantiomeric excess: > 99% by chiral GC

- $^1\text{H}$ -NMR ( $\text{CDCl}_3$ ):  $\delta$  7.16 - 7.32 (m, 4H), 5.74 (d,  $^3J = 9$  Hz, 1H), 5.48 (q,  $^3J = 7.4$  Hz, 1H), 2.98 (m, 1H), 2.87 (m, 1H), 2.62 (apparent ddt,  $^2J = 12.9$  Hz,  $^{333}J = 4.4 / 7.4 / 7.5$  Hz, 1H), 2.04 (s, 3H), 1.81 (apparent ddt,  $^2J = 12.9$ ,  $^{333}J = 7.4 / 7.7 / 8.8$  Hz, 1H).

$^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ ):  $\delta$  169.81 (CO), 143.45 (C-bridge head), 143.11 (C-bridge head), 128.00 (Ar), 126.76 (Ar), 124.82 (Ar), 124.01 (Ar), 54.73 (HCN), 34.07 ( $\text{CH}_2$ ), 30.21 ( $\text{CH}_2$ ), 23.47 ( $\text{CH}_3\text{CO}$ ).

**Example 7**  $\text{R}^1 = 4\text{-bromophenyl}$ ,  $\text{R}^2 = \text{R}^3 = \text{H}$ ,  $\text{R}^4 = \text{CH}_3$

- A. Sodium acetate (250 g, 3.0 mol) was added to a solution of 4-bromoacetophenone (500 g, 2.5 mol) in methanol (1 L) followed by hydroxylamine hydrochloride (192 g, 2.76 mol). After stirring for 20 h, water (1 L) was added over 1 h, and then the reaction stirred for a further 2 h. The resultant solid was filtered and washed with water (2 x 200 ml) and dried to give 4-bromoacetophenone oxime (561 g).
- B. Acetic anhydride (165 ml) and acetic acid (100 ml) were added to a suspension of 4-bromoacetophenone oxime (150 g, 0.7 mol) in toluene (1.5 L) and allowed to stir under nitrogen. Fe powder (78.3 g, 1.4 mol) was then added and the mixture heated at 70-75 °C

for 20 h. The reaction was then cooled and filtered through Celite to remove solid residues. These residues were washed with toluene (3 x 200 ml). The combined organic extracts were then diluted with dichloromethane (1 L) and washed with 2 M NaOH (3 x 1 L) such that the aqueous phase remained at pH 14. This final biphasic mixture was then  
5 allowed to stir for 0.5 h. The organic phase was then separated, dried ( $\text{MgSO}_4$ ) and evaporated to a volume of 1 L and allowed to crystallise. The solid was filtered to give *N*-acetyl-1-(4-bromophenyl)-1-ethenamine (98.4 g, 63%).

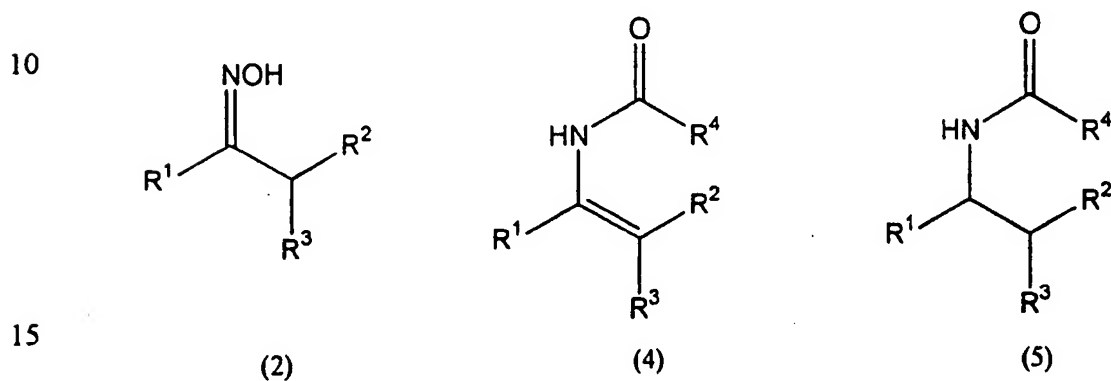
C. Degassed dichloromethane (500 ml) was added to *N*-acetyl-1-(4-bromophenyl)-1-ethenamine (50.0 g, 0.21 mol) and  $[(\text{COD})\text{Rh}(\text{R,R})\text{Me-DuPHOS}]\text{BF}_4$  (0.13 g, 0.2 mmol)  
10 in a 2 L Parr pressure vessel, purged with hydrogen. The reactor then was purged with hydrogen (three times), charged to 1380 kPa (200 psi) hydrogen and allowed to stir for 14 h. Subsequent evaporation of the solvent yielded (*R*)-*N*-acetyl-1-(4-bromophenyl)ethanamine (50.7 g, 100%) with 95.2% enantiomeric excess.

This Example shows that the Br atom is maintained through the various reactions.

CLAIMS

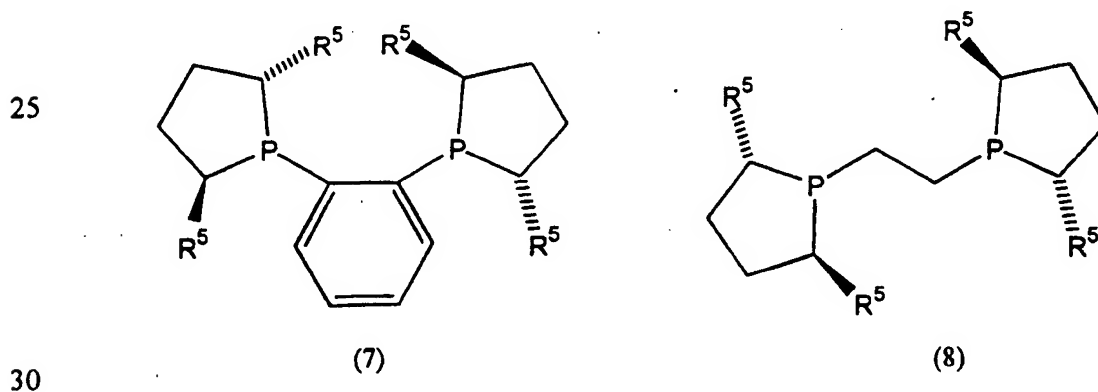
1. A process for the preparation of an enantiomerically-enriched chiral amide (5), which comprises the following steps:

- (a) the reaction of an oxime (2) with a reducing metal  $M^1$  in the presence of an acylating agent  $R^4COX$  (3), where X is a leaving group, to give an enamide of formula 4; and
- (b) catalytic asymmetric hydrogenation of the enamide (4)



wherein  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  are independently selected from H and any organic group of up to 30 C atoms, or  $R^3$  forms a ring or rings together with  $R^1$  and/or  $R^2$ .

2. A process according to claim 1, wherein the catalyst used in step (b) is a complex of a transition metal  $M^2$  and a chiral phosphine ligand.
- 20
3. A process according to claim 2, wherein the ligand is a chiral bis-phosphine of formula (7) or (8)



(or the opposite enantiomer thereof), wherein  $R^5$  is any non-hydrogen organic group.



4. A process according to claim 3, wherein  $R^3$  is  $C_{1-4}$  linear or branched alkyl.
5. A process according to any of claims 2 to 4, wherein  $M^2$  is Rh, Ru or Ir.
6. A process according to any preceding claim, wherein step (a) is conducted in the presence of an acid and a solvent.
- 5 7. A process according to claim 6, wherein  $M^1$  is Fe, the acylating agent is acetic anhydride, the acid is acetic acid, and the solvent is toluene.
8. A process according to any preceding claim wherein the oxime (2) is derived from a carbonyl compound of the formula  $R^1CO-CHR^2R^3$  (1), provided that when  $R^1=H$ ,  $R^2$  and  $R^3$  are different groups and neither is H.
- 10 9. A process according to any preceding claim, wherein  $R^1$  and  $R^3$  are independent such that the carbonyl C atom is not in a ring.
10. A process according to claim 9, wherein  $R^2$  and/or  $R^3$  is H.
11. A process according to claim 9 or claim 10, wherein  $R^1$  is an aryl, heteroaryl or unsaturated aliphatic group.
- 15 12. A process according to claim 9 or claim 10, wherein  $R^1$  is *tert*-alkyl, e.g. *tert*-butyl, or adamantyl.
13. A process according to claim 9 or claim 10, wherein  $R^1$  is trihalomethyl, e.g.  $CF_3$ .
14. A process according to any of claims 1 to 8, wherein  $R^1$  and  $R^3$  form a ring.
15. A process according to claim 14, wherein the ring comprises an indanone nucleus.
- 20 16. A process according to claim 14, wherein the ring comprises a tetralone nucleus, e.g.  $\alpha$ -tetralone or  $\beta$ -tetralone.
17. A process according to claim 16, which is conducted at a temperature below  $20^\circ C$ , preferably at or below  $10^\circ C$ .
18. A process for the preparation of an enantiomerically-enriched chiral amine of the  
25 formula  $R^1-CHNH_2-CHR^2R^3$  (6), which comprises the steps of a process according to any preceding claim and deprotection of the amine functionality.
19. An enamide of formula (4) as defined in claim 12.
20. An enamide of formula (4) as defined in any of claims 13, 15 and 16, wherein  $R^4$  is non-functional  $C_{1-10}$  linear or branched alkyl.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 98/02966

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07C231/18

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	M.J. BURK ET AL.: "A convenient asymmetric synthesis of alpha-1-arylalkylamines through the enantiomeric hydrogenation of enamides" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY., vol. 118, 1996, pages 5132-5143, XP002069947 DC US cited in the application see page -	1
A	US 4 194 050 A (HAZAMA MOTOO) 18 March 1980 cited in the application see page -	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

18 December 1998

Date of mailing of the international search report

04/01/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Pauwels, G

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 98/02966

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4194050 A	18-03-1980	JP 1340659 C	14-10-1986
		JP 52133905 A	09-11-1977
		JP 61006812 B	01-03-1986
		CH 630339 A	15-06-1982
		DE 2718552 A	10-11-1977
		FR 2349567 A	25-11-1977
		GB 1526683 A	27-09-1978
		NL 7704627 A	01-11-1977
		US 4137417 A	30-01-1979
<hr/>			